Volume Management and Resuscitation in Trauma

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Abstract Trauma remains an enormous burden on the American medical system. While patients of all ages sustain severe trauma, it remains the most common cause of death in young adults. Exsanguination from uncontrolled hemorrhage is the leading cause of preventable death among the traumatically injured. The lethal triad of trauma is a culmination of coagulopathy, acidosis, and hypothermia that can rapidly deteriorate and lead to a patient's demise if not treated accordingly. The goal of trauma resuscitation is to prevent or halt this triad while minimizing iatrogenic injury. The provider has many options available in his armamentarium for resuscitation, but each carries its own risks and benefits. Over the past two decades, trauma research has given us a better understanding of and improved management strategies for this triad. This chapter will explore the various resuscitative options available and summarize the most recent literature regarding their use.

Keywords Trauma · Damage control laparotomy · Damage control resuscitation · Massive transfusion

Introduction

Exsanguination from uncontrolled hemorrhage is responsible for nearly 40 % of all trauma deaths [1]. Despite numerous advancements in medical infrastructure and technology, it remains the leading cause of preventable death in this population [2, 3]. Multiple factors contribute to ongoing hemorrhage, thereby increasing the odds of a poor outcome. The time passed before definitive care significantly increases the risk of developing hypothermia, a factor which independently increases mortality [4, 5]. However, hypothermia is not the only mechanism at work; other intrinsic processes are at play [6]. Hyperfibrinolysis, platelet dysfunction, and hypoperfusion have all been implicated as contributors to this “coagulopathy of trauma”, which has been shown to increase coagulation times, and most importantly, mortality in this population [3, 7–10]. From the very beginning, trauma resuscitation has been an evolving science, a science very different than elective surgery, focused on minimizing and preventing the complications from coagulopathy, acidosis, and hypothermia. The goal of resuscitation, therefore, is to address these problems while minimizing additional insults that can spiral out of control in the hemorrhaging patient. This chapter is a comprehensive review of the literature regarding the numerous resuscitative options currently available, as well as, recommendations for resuscitation of the trauma patient.

Crystalloids

The 9th edition of the Advanced Trauma Life Support (ATLS) recommends giving up to 2 L of warm isotonic crystalloid as the initial resuscitative agent [11]. This recommendation is to help maintain perfusion pressure in the

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hypotensive trauma patient especially in centers that do not have rapid access to stored blood products. Infusing higher volumes of crystalloids is not without its complications, although, limiting crystalloid infusion is a practice often easier said than done. Complications from excessive crystalloid resuscitation such as pulmonary edema is well-documented, however, evolving evidence has demonstrated that this practice's impact extends beyond the lungs [12].

The widespread acceptance and employment of damage control laparotomy (DCL) in the treatment of devastating abdominal injuries has revolutionized the care of the severely injured trauma patient. First described in 1993, the tenants of DCL include surgical control of hemorrhage and contamination, deferment of definitive repair until physiologically stable, and temporary abdominal closure [13]. This approach has since been augmented by incorporating damage control resuscitation (DCR) principles, which aim to reverse coagulopathy through the utilization of permissive hypotension, judicious use of isotonic crystalloids, and a balanced approach to blood transfusion [14]. The theoretical objective behind permissive hypotension is to maintain adequate perfusion to vital organs without raising the blood pressure to such a level that clots dislodge, perpetuating further bleeding. The United States military was one of the first to incorporate these objectives into policy, and documented a segmental decrease in mortality among patients who received a massive transfusion each year following its adoption [15]. Many civilian trauma centers have adopted this policy, with subsequent improvement in both transfusion volumes as well as overall mortality [16]. Although promising, no randomized controlled trials have been performed to validate these findings.

Recent studies have investigated the morbidity associated with aggressive fluid resuscitation following DCL including the development of abdominal compartment syndrome and anastomotic leaks following colon resection [17, 18]. One group found the amount of crystalloid infused in the first 24 h to be an independent risk factor for failure of primary fascial closure [19]. As the rate of complications, particularly enteroatmospheric fistulas, is directly proportional to the length of time the abdomen is left open, cautious crystalloid use is advocated [20]. The use of 3 % hypertonic normal saline (HTS) represents one potential solution to limiting the amount of crystalloid administration. One group found reliance on HTS as the sole maintenance fluid following DCL was not only associated with significantly less IVF during the first three post-operative days, but it also permitted surgeons to close the abdomen 100 % of the time compared to a 76 % closure rate in those receiving isotonic fluids [21]. Surprisingly renal function was not significantly affected with this approach, a finding that may be related to hypertonic

saline's ability to blunt the inflammatory response [22]. These findings raise the question as to whether hypertonic saline has a defining role in trauma resuscitation outside of its use in the care of patients with traumatic brain injuries (TBIs) [23].

Given the plethora of complications associated with over-resuscitation, several groups have sought to determine whether an even more conservative approach should be taken. In a prospective randomized manner, one group compared a target systolic blood pressure (SBP) of 70 mmHg with 90 mmHg, a standard resuscitation goal [24]. The authors found that a lower SBP goal significantly reduced transfusion requirements without a concomitant increase in mortality. They concluded that this resuscitative threshold was a safe and viable goal. A second group found similar results when comparing the accepted MAP of >65 mmHg to resuscitation to a MAP of only 50 mmHg [25]. The groups' findings add further support to the concept of permissive hypotension.

Complicating the resuscitation strategy of permissive hypotension is hemorrhage in the setting of a concurrent TBI. Several investigators have documented that even a single episode of hypotension, defined as SBP < 90 mmHg, in severe TBI is associated with a substantial increase in morbidity and mortality [26, 27]. Therefore, in this instance it is recommended to maintain a SBP > 90 mmHg to minimize secondary brain insult. In those TBI patients with intracranial pressure monitors, therapy should also include sustaining a cerebral perfusion pressure (CPP) around 60 mmHg [28]. Although the exact CPP to target is not known critical brain ischemia has been shown to occur in the 50–60 mmHg range [29]. Likewise, aggressively raising the CPP threshold above 70 mmHg, in an attempt to prevent cerebral desaturation, with volume expansion and vasopressors has been associated with deleterious effects, such as ARDS, and should be avoided [30, 31].

Colloids

In no area of resuscitation does the provider have so many different options than in colloids. Hydroxyethyl starch, albumin, and dextran solutions, available in varying concentrations, are vital components of the physician's armamentarium. What makes these solutions invaluable is their ability to remain intravascular and expand the total blood volume to varying degrees [32].

A significant amount of research has focused on the use of 6 % hetastarch as a primary resuscitative agent in trauma patients. Derived from plants, the fluid bypasses the theoretical harm of infection inherent to human-derived solutions such as albumin and blood products [33]. Its smaller volume, and therefore reduced weight, makes it an attractive option for use in the pre-hospital setting and for

military first responders. Results of clinical trials thus far have been conflicting, with some groups touting decreased mortality as compared to a resuscitative strategy based on crystalloids [34, 35], while others have identified several-fold increases in both morbidity, particularly acute kidney injury, and overall mortality [33, 36]. The higher incidence of end-organ injury demonstrated with colloids has been postulated to be a result of a pro-inflammatory state induced by the fluid [22].

Albumin is a colloid derived from human plasma. It is available in varying concentrations from 5 to 25 %. There have been multiple small randomized controlled trials that compared 20 % albumin to hydroxyethyl starch in the treatment of moderate-to-severely injured trauma patients [37]. The majority found albumin to be inferior to the synthetic colloid, particularly with respect to improvements in cardiac index, decreased vasopressor use, and higher PaO₂/FiO₂ ratios [38–40].

Two Cochran Review analyses could not find evidence to conclude that colloid was superior to crystalloids in the treatment of critically ill patients [41, 42]. The Saline versus Albumin Fluid Evaluation (SAFE) Study, a double-blind multi-center randomized controlled trial, essentially found no difference in mortality between the colloid and crystalloid groups [43]. However, in subgroup analysis the authors discovered slightly higher mortality (RR 1.36) among trauma patients who received 4 % albumin as compared to NS. Overall though the findings from this study are difficult to interpret, as the albumin group received significantly higher amounts of non-study fluid [normal saline and packed red blood cells (pRBCs)] than albumin during the first four hospital days.

Despite these conflicting results, many clinicians believe albumin, especially the highly concentrated form, is a viable option for resuscitation of trauma patients, particularly for its anti-inflammatory properties. In *ex vivo* studies, 25 % albumin has been shown to inhibit neutrophil adhesion to endothelial cells, an important step in the process of polymorphonuclear (PMN) cell translocation [44]. This process has also been shown to reduce the amount of neutrophil sequestration and activation that ultimately culminates in a pro-inflammatory state leading to end-organ injury [22]. As with other colloids, albumin is advantageous over crystalloids due to its small size and weight. Available in 100 cc bottles, it is easily transported to the scene of injury for pre-hospital resuscitation. These characteristics, combined with its proven ability to expand the intravascular space, have made it the ideal fluid for resuscitation in combat by the Committee for Tactical Combat Casualty Care [45].

Dextran is a synthetic colloid that is often combined with 7.5 % saline for use as a hypertonic resuscitative agent. By increasing osmotic pressure, hypertonic-saline

dextran (HSD) has been shown to be superior to other colloids in increasing intravascular volume [32]. Multiple randomized controlled trials have been performed to test whether this benefit leads to an improvement in patient outcome. The trials have offered conflicting results based on the population studied [46]. In summary, non-TBI patients with active bleeding may benefit, while those with severe head injuries may do worse. These findings make it difficult to recommend the use of this agent in the multi-trauma patient with a TBI.

With so many options and conflicting data it is difficult to determine whether colloids are superior to crystalloids during initial resuscitation. Two recent Cochrane Review analyses were unable to definitively determine whether one colloid was superior to another [42], or even superior to crystalloids [41] in the treatment of critically ill patients. Recently the CRISTAL study sought to answer the question once and for all. It was a large multicenter randomized controlled trial that compared crystalloids (LR, NS, 3 % NS) versus colloids of all types (gelatins, dextran, hydroxyethyl starch, albumin) and strengths in the resuscitation of hypotensive ICU patients. The investigators found that although the colloid group received significantly less fluids and required less ventilator and hemodynamic assistance, there was no difference in hospital or 30-day mortality. When the patients were followed out to 90 days, however, a slight survival advantage was detected. Although encouraging, this study is not applicable to the trauma population, as the majority (55 %) of the patients' underlying problem was sepsis, with trauma accounting for only 5 %. Until a large randomized study of trauma patients is performed, the choice of fluids remains unclear.

Blood Products

From the initial ATLS guidelines that emphasized aggressive transfusion of crystalloids at the expense of blood products, the paradigm of fluid management has completely changed its priorities with an emphasis on early correction of coagulopathy and avoidance of over-transfusion. Thanks to widespread acceptance of continuously evolving practice patterns, such as massive transfusion protocols and DCR, patients are receiving life-saving blood products in a timely and judicious manner. The development of new diagnostic modalities, such as TEG, has allowed for a more individualized-approach to resuscitation. Initial studies describing the use of rapid-thrombelastography (r-TEG) at the point of care have been promising; numerous studies have demonstrated r-TEG can accurately diagnose coagulopathies in a fraction of the time required for standard coagulation profiles [47, 48]. Others have advocated its use as an adjunct in determining adequate resuscitation [49], and demonstrated improved

survival as compared to standard massive transfusion protocols [50]. The relative benefits of the test have not been sufficient to justify its expense for many small non-academic centers, so its current availability is limited to larger tertiary centers. In the following section we offer one transfusion protocol for the traumatically injured.

Current transfusion protocols have evolved from the days of giving two units of pRBCs and waiting for a response. Due in no small part to the combat injuries sustained in Iraq and Afghanistan, the United States military has contributed significantly to the concepts of massive transfusion and balanced resuscitation. Over the course of the conflicts military physicians continuously modified their practice patterns; massive transfusions accounted for nearly 50 % of all transfusions in 2011 [51]. Fresh whole blood was utilized in situations when the demand for blood components outnumbered its pre-packaged supply [51–53]. They found that nearly one-third of their patients were coagulopathic on admission, and by increasing the ratio of both FFP and platelets to pRBC, they were able to decrease mortality rates despite increasing injury severity scores [54]. These concepts have been adopted by civilian centers and have ignited a mission to find the optimal resuscitative ratio.

Massive transfusions have long been an important component of the care for the traumatically injured, but it has only been within the last decade that trauma centers have implemented formal protocols governing its use. The idea behind the mass transfusion protocol (MTP) is to quickly identify patients that will likely require more than four units of pRBC and have the blood products thawed and ready for use. The results thus far have been mixed. The studies have uniformly documented a significant decrease in blood availability time, however, this has not always translated into a reduction in component use or mortality [55–57]. One investigator discovered an interesting trend when reviewing his institution's outcomes before and after the implementation of a MTP. He found that although there was no difference in mortality among patients who received a MT, survival was doubled in patients who received a "sub-MT", i.e., greater than six but less than 10 units of pRBCs [58]. Further investigation revealed that these patients received significantly more FFP and platelets in the first 6 h, at higher ratios, following institution of the MTP. This study lends evidence in support of early correction of coagulopathy, one of the primary goals of DCR.

Fresh frozen plasma is obtained via apheresis of whole blood and frozen within 8 h [59]. It contains all the clotting factors, fibrinogen, proteins C and S, and albumin. It is available in 250 and 500 cc bags that must be thawed and used within 24 h or it becomes classified as frozen plasma, which has been shown to contain significantly less clotting

factors and a diminished ability to restore intravascular volume [60]. FFP has also been shown to be significantly less immunogenic than pRBCs [61, 62], and decreases vascular leakage through stabilization of the endothelial membrane [60].

Multiple studies have sought to determine whether FFP's benefits in the laboratory and the deployed setting are translatable to civilian trauma, and if so, to determine the optimal transfusion ratio. Holcomb et al. [63] was one of the first to address this problem. In his retrospective analysis of multiple level 1 trauma centers he found that a FFP:pRBC ratio greater than 1:2 was associated with significantly lower thirty-day mortality in patients who were severely injured (mean ISS 32) and received a mass transfusion. Other investigators have corroborated these findings with even higher FFP:pRBC ratios [64–66], while another was able to demonstrate an early survival benefit with a balanced approach regardless of admission coagulopathy [67]. When investigators looked at trauma patients who received a sub-massive transfusion the results became more complicated. Some investigators identified early high ratio transfusion as an independent predictor of survival, both early and late, without an increase in the incidence of transfusion-related complications such as sepsis, MODS, and venous thromboembolism [68]. Others have published results suggesting the practice is not beneficial, and even harmful, to patients in this population [69, 70]. To add clarity to these conflicting results, the Cochrane group has launched its own review, with results expected soon [71]. Based on available data, the goal for massive transfusion patients is to transfuse to a FFP:pRBC ratio of nearly 1:1, while in patients receiving less than 10 units of pRBC/24 h a more conservative approach of 1:2 should be pursued.

Platelets are another blood component that has been heavily investigated in the recent literature. Although a dedicated analysis failed to demonstrate a correlation between admission platelet count and mortality, an association was discovered between the count and early transfusion requirements [72]. Encouraged by additional evidence that platelets' contribution to the coagulopathy of trauma may be more qualitative than quantitative [9, 73], investigators set out to determine if the benefit of the high transfusion ratios seen with FFP also hold true for platelets. Several multicenter analysis have demonstrated a survival advantage, at 24 h as well as 30 days, in massively transfused patients who received a platelet:pRBC ratio > 1:1.5 [63, 64, 74]. This advantage was additive when combined with a high FFP:pRBC ratio, specifically among patients with exsanguinating truncal hemorrhage. The investigators also noted improvements in ventilator-free days as well as ICU and hospital length of stays. Others have found no difference in mortality after adjusting for confounders [57, 70]. The push for a balanced platelet transfusion

protocol has not been born out in the literature. An optimal approach would be to transfuse platelets at a ratio near 1:3.

Historically pRBCs have been the primary blood component utilized by trauma providers attempting to actively replace the blood loss of the hemorrhaging patient. To produce a 300 cc unit of pRBCs, fresh whole blood must undergo extensive processing. Immediately upon extraction the blood must be mixed with a citrate–phosphate–dextrose solution to prevent coagulation [75]. It is then centrifuged down and the buffy coat is removed. These procedures extend the shelf-life of blood to 42 days [76]. Leukoreduction is an additional step where white blood cells are removed by specialized filters, decreasing the overall burden to less than 0.1 % [77].

Transfusion of blood products, however, is not without complications. The processes of preparation and storage of blood products have been associated with the development of transfusion-related complications such as transfusion-related lung injury (TRALI), the systemic inflammatory response syndrome (SIRS), and multi-organ failure (MOF) [78, 79]. Data has linked these complications to neutrophil priming particles such as microparticles (MP's) and lysophosphatidylcholine (lyso-PC's) that have been shown to accumulate over time [61, 80]. Aged blood has also been shown to be less efficient in coagulation, as measured by the activated coagulation time [81]. All of these factors may contribute to its increased mortality when used in the hemorrhaging trauma patient [82]. Pre-storage procedures such as leukoreduction and washing have been shown to decrease the inflammatory response, making the transfusion of aged pRBCs a viable option for these patients [77, 83].

Through the various mechanisms described above, as well as its proven role in T cell suppression [84], the number of units of pRBCs transfused has been shown to be an independent risk factor for mortality in this population [77, 85]. This underscores the importance of determining the optimal transfusion threshold. Several investigators have attempted to answer this question. Ryan et al. retrospectively reviewed admission hematocrit (HCT) with the need for transfusion and vasopressor support among trauma patients requiring emergency surgery. The authors found that in this cohort of patients admission HCT as low as 37 % was predictive of the need for additional hemodynamic support [86]. Interestingly, they found that traditional markers of shock, including pulse and respiratory rate, were not predictors for necessitating further hemodynamic support. A study by Long et al. examined postoperative HCT levels and survival among trauma patients who received a massive transfusion. They found that patients who were transfused to physiologic levels (HCT 29–39 %) postoperatively had better short term survival compared to those patients transfused to supraphysiologic

levels, >39 % [87]. These studies are limited by their retrospective nature, finite population (patients who required emergency surgery), as well as their lack of long-term outcomes, however, they provide a basis for further prospective analysis for trauma transfusion thresholds. The transfusion of pRBCs is not without significant risk of adverse events such as TRALI and MODS, and this risk appears to be proportional to the amount and the age of the blood transfused. However, one should not withhold transfusion in the appropriate patient. The combination of indices, such as vital signs, lactate, pH, and base deficit, along with clinical judgment is the best approach to transfusing a hemorrhaging trauma patient.

Two relatively new hemostatic adjuncts, recombinant Factor VIIa (rVIIa) and Tranexamic Acid (TXA), have been used more frequently in recent years. Studies published from the U.S. military conflicts in Iraq and Afghanistan have added to the increased application of these products in the trauma population. Retrospective data on rVIIa from massively transfused combat casualty patients demonstrated both short and long-term survival, decreased transfusion requirements, and similar rates of inflammatory or thromboembolic complications in patients who received rVIIa compared to those who did not receive the drug [88, 89]. The CONTROL trial was a civilian phase III prospective, randomized, placebo-controlled multicenter trial evaluating rVIIa in both blunt and penetrating trauma [90]. Over 500 patients were enrolled from 150 hospitals across the world. Unfortunately, the study was stopped early after preliminary data demonstrated the futility in meeting the primary endpoint of decreased mortality, as the observed mortality was significantly lower than expected. From the analyzed data collected, however, the subgroup of blunt trauma patients receiving rVIIa received fewer units of pRBCs and FFP than the subgroup of blunt trauma patients receiving the placebo drug. The authors also found that there was no difference in adverse events between the rVIIa and placebo groups. With the available published literature, use of rVIIa should be limited to the ongoing hemorrhaging trauma patients receiving a massive transfusion.

TXA is an antifibrinolytic that binds to plasminogen and prevents its conversion to plasmin [91]. Interest in it arose as a potential adjunct to correcting the coagulopathy of trauma after years of data from cardiac surgery demonstrated decreased fibrinolysis with decreased blood loss and subsequent transfusion requirements, associated with TXA's use [92, 93]. The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2 trial (CRASH-2) was the first large multi-center, randomized, prospective placebo-controlled trial that evaluated TXA's use in actively hemorrhaging trauma patients [94]. Over 20,000 patients were enrolled from 270 hospitals

worldwide. The primary endpoint was in-hospital 30-day mortality. There was a significant reduction in all-cause mortality in the TXA group ($p = 0.0035$), as well as death due to hemorrhage ($p = 0.0077$) and no difference in vascular occlusive events ($p = 0.096$), although these benefits were only realized if TXA was administered within 3 h of injury. However, there was no difference in transfusion rates between the TXA and placebo groups.

The Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) study was a retrospective comparison of transfusion requirements, thromboembolic events, and mortality between combat injured who received TXA and at least one unit of pRBC's versus those injured who received at least one transfusion and no TXA [95•]. Similar to the CRASH-2 trial, patients receiving TXA had a mortality rate that was significantly lower than those who did not receive TXA, despite the fact that the TXA group was more severely injured, coagulopathic, and hemodynamically unstable. This survival advantage was more pronounced in the subgroup of patients receiving a massive transfusion. The investigators also discovered significantly higher rates of thromboembolic events and blood product usage in the TXA group, contradictory to the findings in the CRASH-2 trial, which were attributed to the higher severity of injury in the combat wounded.

The Cochrane investigators recently performed of a review of the two randomized clinical trials that compared TXA versus placebo in the treatment of traumatic injuries and concluded that the mortality benefit from uncontrolled hemorrhage is extremely time dependent [96]. If the drug is given within 3 h of injury the relative risk reduction is 21 %, whereas administration after that time period incurs a relative risk *increase* of 44 %. Based on the available data in the trauma literature, TXA should be considered as a hemostatic agent in the massively transfused patient if given within 3 h of injury. Administration outside that window incurs an increase in thromboembolic events without a survival benefit.

Conclusion

DCR has revolutionized how we approach the hemorrhaging trauma patient. It is based on the principles of judicious crystalloid use, tolerance of permissive hypotension, and balanced transfusion of blood products. When presented with an actively bleeding patient, resuscitation with no more than 2 L of warmed isotonic crystalloid is an appropriate first step. The complications related to over-resuscitation are well established. However, the maximal threshold for total volume of crystalloid resuscitation has not yet been elucidated in the literature, therefore a

definitive recommendation cannot be given. Instead, physiologic parameters such as pulse rate, blood pressure, hemoglobin level, lactate, pH, and base deficit combined with sound clinical judgment should guide one's resuscitation. If the patient fails to respond to the initial bolus, one should identify the source of bleeding and begin transfusion of blood products in a roughly 1:1:1 ratio. The decision to activate a massive transfusion protocol should be made early. Once activated, consider administering adjuncts such as TXA or rVIIa early in the resuscitative process.

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Compliance with Ethics Guidelines

Conflict of Interest Matthew J. Bradley and Vincent S. Nelson declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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